35. (NEW) The thrombin preparation of claim 18 wherein the noncovalently binding inhibitor of thrombin activity is benzamidine.

36. (NEW) The thrombin preparation of claim 18 wherein the noncovalently binding inhibitor of thrombin activity is p-aminobenzamidine.

37. (NEW) The thrombin preparation of claim 18 wherein, after 12 months of storage at 20-25 °C, the thrombin maintains at least 70% of its original level of activity.

38. (NEW) The thrombin preparation of claim 18 wherein the thrombin preparation has a pH of from 5.0 to 8.0.

REMARKS

Restriction Requirement

Claims 20-34 were originally pending in this application. (Preliminary Amendment submitted March 16, 2001.) The Office required restriction under 35 U.S.C. § 121 between Group I (claims 18 and 19), Group II (claims 20-31), Group III (claims 32 and 33), and Group IV (claim 34). (Office Action at page 2.) Applicants confirm the provisional election, with traverse, of Group I (claims 18 and 19), made in a telephone conversation with the Examiner on November 8, 2001. (Office Action at page 3.)

Section 803 of the M.P.E.P. states that "[i]f the search and examination of the

the merits, even though it includes claims to independent or distinct inventions." (M.P.E.P. § 803, emphasis added.) Applicants respectfully submit that this policy should apply to this application in order to avoid unnecessary delay and duplicative examination.

A search on all of the claimed subject matter can be made without undue burden because a literature search for the four groups would be coextensive. To illustrate this point, Applicants note that claims 32 and 33 (Group III) depend directly or indirectly from claim 18 (Group I). Therefore, a search for a "method of using the thrombin preparation of claim 18" would involve a search for the thrombin preparation of claim 18. Claim 34 (Group IV) similarly depends, through claim 31, on claim 20 (Group II). In addition, the subject matter of Groups II and III falls within the same class (424). Thus, Applicants respectfully request the Office to rejoin the groups.

Finally, according to 37 C.F.R. § 1.141(b) and M.P.E.P. § 821.04, when the Office determines that claims drawn to a product are allowable, claims directed to methods of using or processes of making the product may be rejoined. Thus, if the Office maintains this restriction requirement, Applicants respectfully request that the Office rejoin the process of making and method of use claims 20-34 once the Office determines that claims 18, 19, and 35-38 are patentable.

Status of the Claims

The Office has withdrawn claims 20-34 from consideration due to the above restriction requirement. Thus, claims 18 and 19 are presently under examination. Applicants have amended claim 18 and added new claims 35-38. Claim 18 as

binding inhibitor of thrombin activity as stabilizer, wherein the thrombin preparation is suitable for therapeutic purposes." Such a preparation could be used as a hemostatic, or a constituent of tissue glue, as recited in claims 32-34, or for another therapeutic use. New claims 35-38 recite thrombin preparations with a particular pH or thrombin activity range, or containing a particular noncovalently binding inhibitor of thrombin activity.

Amended claim 18 and new claims 35-38 are supported by the application as a whole. Support for amended claim 18 may be found, *inter alia*, at page 1, lines 1-13, page 5, lines 25-28, and page 7, lines 5-22, of the specification. Claims 35 and 36 are supported in the specification at page 6, lines 7-15, and claim 10 as filed, among other locations. The specification supports claim 37, *inter alia*, at page 3, lines 5-9, page 6, lines 7-28, and in tables 4 and 5. Claim 38 is supported at page 5, lines 4-7, and in claim 7 as filed, among other locations. Therefore, Applicants submit that these amendments do not introduce new matter into the specification or require a new search of the art. Applicants respectfully request their entry.

Objection to the Specification Arrangement

The Office objected to the specification for lacking section headings. (Office Action at page 4.) Applicants note that the present Office Action and M.P.E.P. § 608.01, ¶ 6.01, state that these headings are preferred, not required. Further, the German priority document does not contain such headings. Thus, Applicants have not corrected the specification.

Rejection of claim 18 under 35 U.S.C. § 112, second paragraph

The Office asserted that claim 18 is indefinite because it is unclear that thrombin

claimed thrombin preparation. (Office Action at page 5.) Applicants submit that this rejection is now moot in view of the amendment to claim 18, adding thrombin to the body of the claim. Because one of skill in the art would recognize that thrombin is a part of a "thrombin preparation," simply adding thrombin to the body of claim 18 does not change the scope of the pending claims.

Rejection of claim 18 under 35 U.S.C. § 102(e)

The Office rejected claim 18 as allegedly anticipated by Hanada et al. ("Hanada"; U.S. Patent No. 5,945,103). (Office Action at pages 5-6.) Applicants respectfully traverse this rejection.

In order for a piece of prior art to anticipate a claim, it must teach each and every element of that claim either explicitly or inherently. *See, e.g., Verdegaal Bros. v. Union Oil Co. of Cal.*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Hanada does not teach each and every element of claim 18 as amended because it does not teach a "thrombin preparation comprising thrombin and a noncovalently binding inhibitor of thrombin activity" that is also "suitable for therapeutic purposes."

Instead, in Hanada, a noncovalently binding inhibitor of thrombin, such as benzamidine or p-aminobenzamidine, is added only during trialkyl phosphate treatment of a thrombin solution, one of a series of treatments performed before thrombin is made into a final preparation. (Hanada at col. 3, line 62, to col. 4, line 67.) The trialkyl phosphate treatment preparation of Hanada has not yet been subjected to dry heating to inactivate pathogenic viruses. (Hanada at col. 4, lines 12-67, and col. 5, Example 1.) Because it may contain viral pathogens, it is not suitable for therapeutic use and cannot

preparation of Hanada cannot anticipate claim 18 because it no longer contains the noncovalently binding inhibitor of thrombin activity, such as benzamidine or p-aminobenzamidine. (Hanada at col. 4, lines 46-67, and col. 5, Example 1.) In Hanada's method, a cation exchange procedure is performed after trialkyl phosphate treatment such that the inhibitor, as well as the trialkyl phosphate and surfactant, are removed prior to dry heating and are thus excluded from the final preparation. (*Id.*)

For these reasons, Hanada cannot anticipate claim 18. Thus, Applicants respectfully request the Office to withdraw this rejection.

Rejection of claims 18 and 19 under 35 U.S.C. § 103(a)

The Office rejected claims 18 and 19, asserting that they are obvious over Hanada, in view of Brezniak et al. ("Brezniak"; *Blood Coagulation and Fibrinolysis* 5: 847-8 (1994)) and Altshuler (U.S. Patent No. 4,363,319). (Office Action at pages 6-8.) Applicants also traverse this rejection.

First, to establish a *prima facie* case of obviousness, there must be a suggestion or motivation in the reference itself, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference, as well as a reasonable expectation of success in doing so. M.P.E.P. §§ 2142-3. Furthermore, both the motivation to modify the reference and the reasonable expectation of success must be found in the prior art, not in an applicant's disclosure. M.P.E.P. §§ 2142-3; *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The Office relies on Hanada for a teaching of noncovalently binding inhibitors of thrombin activity, amino acids, sodium chloride, and sugar alcohols as stabilizers.

therapeutic purposes containing benzamidine or p-aminobenzamidine, or another noncovalently binding inhibitor of thrombin activity. Because benzamidine or p-aminobenzamidine is only used during trialkyl phosphate treatment, Hanada provides no motivation to include these substances in the final preparation. Moreover, the Office has presented no teaching absent Applicants' specification to suggest that a thrombin inhibitor could be added to a thrombin preparation suitable for therapeutic purposes without significantly affecting the thrombin activity of the preparation and thus adversely affecting its usefulness. Brezniak and Altshuler do not remedy this deficiency as they do not discuss such inhibitors at all.

Second, the Office relies on Brezniak and Altshuler for a teaching of a soluble calcium salt as a stabilizer, such as calcium chloride. (Claim 19.) However, Brezniak teaches away from the instant claimed invention by suggesting that calcium chloride is an ineffective stabilizer of thrombin. For example, Brezniak, at page 847, in the first full paragraph of column 2, states that thrombin was more active in sodium chloride than in calcium chloride, and that the "greater stability in NaCl must be attributed to increased thermal stability to denaturation." Moreover, Applicants cite an article by B.H. Landis et al., which teaches that calcium salts reduce the thermal stability of thrombins. (Specification at page 6, lines 12-20.) Thus, these articles teach that calcium salts do not act as adequate thrombin stabilizers. Brezniak and Landis therefore provide motivation to omit calcium salts where possible, not to include them. The Federal Circuit has repeatedly recognized that proceeding contrary to the teachings of the art represents "strong evidence of unobviousness." *In re Hedges*, 228 U.S.P.Q. 685, 687

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(Fed. Cir. 1986); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303, 312 (Fed. Cir. 1983).

The Office cites column 2, lines 12-17, of Altshuler for a teaching of a calcium salt stabilizer. These lines refer to the use of calcium chloride in a dry or powdered thrombin preparation. However, Altshuler points out at column 2, lines 17-39 that such dry or powdered preparations are not sufficiently stable in liquid form to be therapeutically useful, as required by the instant claim 19. For example, Altshuler states that nobody had "satisfactorily devised a method or formulation of thrombin by which it can be prepackaged, sealed and stored in solution form for subsequent application to a wound." (Altshuler at col. 2, lines 22-26.) Thus, Altshuler similarly teaches away from Applicants' claims by showing that calcium chloride and other compounds such as glycine do not adequately stabilize thrombin in the liquid state.

Finally, the Office contends that "it is *prima facie* obvious to combine two or more ingredients useful for the same purpose in order to form a third composition which is useful for the same purpose." (Office Action at page 7.) However, the Federal Circuit has repeatedly stated that to make a *prima facie* case of obviousness, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected *these components in the manner claimed*." *In re Lee*, No. 00-1158, Slip op. at 8 (Fed. Cir. Jan. 18, 2002), quoting *In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000) (emphasis added). Applicants submit that the need for such findings is particularly great where the cited references suggest that one or more ingredients may not, in fact, be useful.

For these reasons, Applicants submit that the combination of Hanada, Brezniak, and Altshuler does not render claims 18 and 19 obvious. The Office has not met its burden to establish a *prima facie* case of obvious meeting the substantial evidence standard required by the Federal Circuit. *See In re Zurko*, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001). Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: April 23, 2002

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APPENDIX TO AMENDMENT OF APRIL 23, 2002

Version with Markings to Show Changes Made

Amendments to the Claims

18. (AMENDED) A thrombin preparation comprising thrombin and a noncovalently binding inhibitor of thrombin activity as stabilizer, wherein the thrombin preparation is suitable for therapeutic purposes.

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